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Short Communication *مراسلة قصيرة*

Synthesis and Dethiation of 5- Phenyl -3- thioxo-2,3-dihydro-1H-2,4-benzodiazepine -1- one

تحضير 5 – فنيل – 3 – ثيوكسو – 3,2 – ثنائي هيدرو – 4,2 – بنزوديأزبين – 1 – أون وإزالة عنصر الكبريت منه

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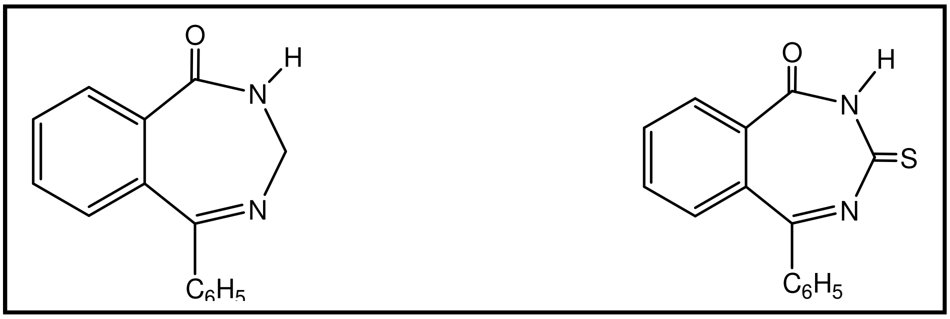
Abstract

The synthesis and characterization of 3-thio-2,4- benzodiazepine -1-one (II) through reaction of o-benzoylbenzoyl chloride with thiourea, and its dethiation to 2,4-benzodiazepine-1-one (III) is described.



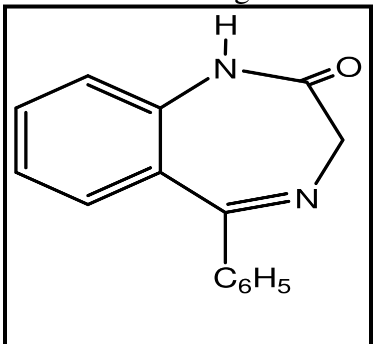
ملخص

تم وصف وتحضير وتمييز ٣ - ثيو-٢،٤- بنزودايأزبين -١-أون (II) من خلال تفاعل أرثو-بنزويل كلوريد البنزويل مع ثيويوريا وإزالة الكبريت من هذا المركب لإنتاج ٢،٤-بنزودايأزبين -١- أون (III) كأحد المركبات المؤثرة على الجهاز العصبي.

Introduction

Despite the fact that 2,4-benzodiazepine-1-one (III) has impressive neurobiological characteristics similar to the known 1,4-benzodiazepines (I) [1,2,3], there are limited numbers of publications regarding the synthesis of 2,4-benzodiazepine derivatives. Such compounds have been synthesized via aza-Wittig methodology [4] which was utilized for preparation of natural antibiotic DC – 81 [a derivative of 1,4-benzodiazpine-5-one] by Molina and co-workers [5]

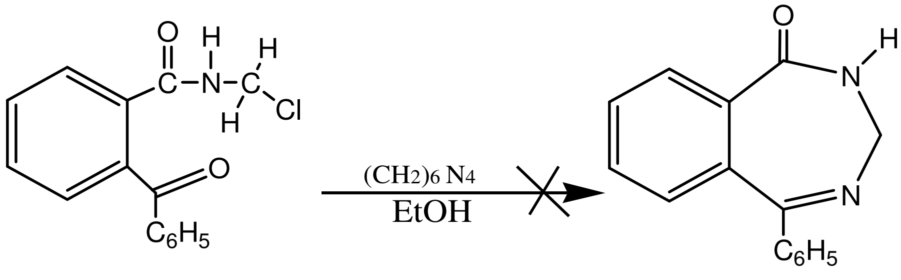
Golik has reported the synthesis of 2,4-benzodiazepine-1-one (III) via reaction of chloromethyl derivative (IV) with ammonia in dioxane [6]. The reported yield for some of these derivatives was as low as 12%. Therefore, due to their biological significance as central nervous system (CNS) depressant [7–10], we are tempted to develop an efficient method for improving such research results through different strategy.



I

Results and Discussion

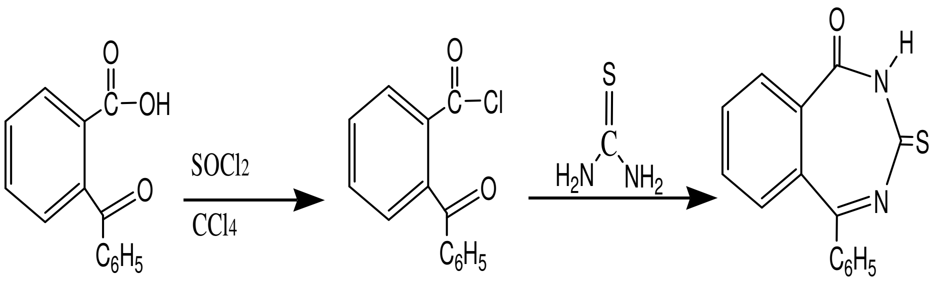
An attempt was made to prepare compound (III) through the reaction of N-chloromethyl-(2-benzoyl) benzamide (IV) with hexamethylenetetramine which is a successful method for preparation of the derivatives of 1,4-benzodiazepines in excellent yields [5]. Unfortunately, such approach was found to be unsuccessful. It seems that the cyclization of the seven membered ring in case of 2,4-benzodiazepine is not successful via compounds (IV) as starting materials, due to the symmetry matching (the carbon atom attached to chlorine in compound (III) is sp^3 hybredized as well as nitrogen atoms in hexamethylenetetramine reagent). These negative results may explain the reason of the poor yield in case of cyclization of (VI) via reaction with aqueous ammonia in dioxane [11]



IV III

Scheme 1

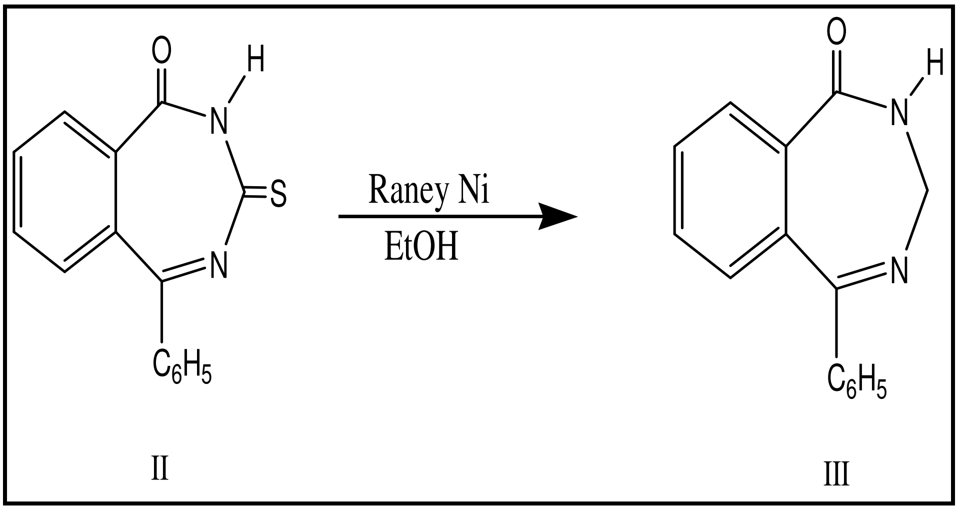
Thereafter, the attention was aimed to prepare o-benzoylbenzoyl chloride (VI) from o- benzoylbenzoic acid (V) through treatment with thionyl chloride to furnish compound (II). Without further purification, compound (VI) was treated with thiourea in benzene to give compound (II) in 7.2% yield. In an attempt to increase the yield, compound (VI) was treated with thiourea at higher temperature (135°C) to produce compound (II) in a relatively good yield of 36% (Scheme 2)



V VI II

Scheme 2

Dethiation of compound (II) by means of Raney Nickel yielded a mixture of compounds. The crude reaction products were isolated by preparative plate chromatography (2:3 (v/v) ether/petroleum ether) to yield 5-phenyl-2,3-dihydro-1-H- 2,4- benzodiazepine-1- one (III) (30%) [m.p. 213 – 214°C] from dioxane (Scheme 3).



Scheme 3

Experimental

Melting point are uncorrected. ^{1}H – NMR spectra were recorded at VarianT-60 instrument with TMS as an internal standard. Signal positions are given in ppm on the δ-scale. IR spectra (KBr disk) were recorded at Perkein Elmer M 257 spectrophotometer (absorptions in cm^{-1}).

o- benzoylbenzoyl chloride (VI).

To a stirred solution of 5g (0.022 mol) of o- benzoylbenzoic acid (V) and 200mL of dry benzene, 1.87g (0.026 mol) of thionyl chloride was added. The reaction mixture was refluxed for 3 hours. The solvent was removed under vacuum gave an oily residue 5.75g. (96%).

5- Phenyl-3- thioxo-2,3-dihydro- 1H- 2,4-benzodiazepin-1-one (II)

Procedure A:

A mixture of 3 g (0.013 mol) of o-benzoylbenzoyl chloride, 1g (0.013 mol) of thiourea and 150 mL of dry benzene was refluxed for 4 hours. The reaction mixture was filtered. Evaporation of benzene under reduced pressure yielded an oily residue which was dissolved in 3 mL mixture of benzene/ acetone (2:1) and chromatographed on silica gel column using benzene/ acetone mixture (2:1) as eluant. The solvents were removed *in vacuo* yielded a solid substance, which on recrystallization from benzene furnished 0.25g (7.2%) of (III): mp 213 – 214^{o}C; ^{1}H-NMR ($CDCl_3$) δ_H: 8.65 – 7.78 (m,9H), 9.4 (s, ^{1}H) ppm.
Anal. Calcd. For $C_{15}H_{10}N_2OS$: C, 67.65; H,3.78; N, 10.52; S, 12.04 Found: C, 67.40; H, 3.86; N, 10.46 S; 11,99.

Procedure B

A mixture of 2.0g (0.009 mol) of o- benzoyl benzoyl chloride and 0.66g (0,009 mol) of thiourea was heated for 1 hr at 135 ^{o}C. After cooling, the solid residue was dissolved in 30 mL chloroform and washed with 10 mL of 5% aq. $NaHCO_3$, the organic layer was dried and the solvent was removed *in vacuo*. The resulting oil was dissolved in 5 mL benzene/ acetone (2:1) mixture and chromatographed on a silica gel column using benzene/acetone mixture (2:1) as eluant. Evaporation of the solvent i*n vacuo* yielded a solid substance which on recrystallization from benzene gave 0.86 g (36%) of (II); the same results were obtained as in procedure A.

5- Phenyl-2,3- dihydro - 1H- 2,4 - benzodiazepine -1-one (III)

To a stirred solution of 1.5 g of Raney nickel and 9 mL 95% ethanol, 0.5 g (0.002 mol) of compound (II) was added. The reaction mixture was refluxed for 1 hour, then allowed to cool. The catalyst was filtered off and ethanol was removed *in vacuo*. Residual oil was separated by silica gel preparative plate [2: 3 (v/v) ether/ petroleum ether] yielded 30% of 5-phenyl-2,3- dihydro -1H -2,4 - benzodiazepine -1-one (III): mp 212.5-

214°C, [Lit. (1), 214°C (from dioxane)]; ^{1}H - NMR (DMSO - d_6) δ_H: 8.95 (s, 1H), 8.2 – 7.1 (m, 9H), 4.08 – 4.00 (s, 2H) ppm.

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